RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL

TITLE: Dual Antiplatelet Therapy Acetylsalicylic Acid Dosing: A Review of the Clinical Effectiveness and Harms

DATE: 14 March 2017

CONTEXT AND POLICY ISSUES

Acute coronary syndromes (ACS) continue to be the worldwide leading cause of adult mortality and morbidity.[1] Patients with ACS or stable angina are commonly treated with percutaneous coronary intervention (PCI) and stenting to slow coronary artery disease progression and prevent major cardiac events.[2] The risks of PCI with stenting include thrombotic complications of acute closure and stent thrombosis. Antiplatelet therapeutics have become an integral part of this management approach to prevent activation of the thrombotic cascade and these subsequent complications.[1-3]

Dual antiplatelet therapy (DAPT) is the most common therapeutic option for patients following PCI.[1] DAPT consists of aspirin (acetylsalicylic acid, ASA) in combination with clopidogrel (an irreversible P2Y12 inhibitor), prasugrel (an irreversible P2Y12 inhibitor), or ticagrelor (a reversible P2Y12 receptor antagonist).[1] In particular, ASA with clopidogrel has demonstrated prevention of thrombotic events in patients undergoing PCI and has represented the standard of care for many years.[3] ASA itself has been a cornerstone of antiplatelet therapy for many years offering cardioprotective effects through irreversible inhibition of cycloxygenase-1 and subsequent downstream reduction of thrombus formation.[4]

Clinically effective and safe DAPT dosing requires a balance between thrombotic risk with inadequate inhibition and bleeding risk with potent inhibition for this patient population.[1] A previously published CADTH technology report, from November 2010, reviewed the evidence for different ASA doses as part of DAPT as one objective.[5] The purpose of this report is to retrieve and review current existing evidence on the clinical effectiveness and safety of a range of ASA doses as a component of DAPT for patients following PCI with stenting.

RESEARCH QUESTION

What is the comparative clinical benefit and harm of different doses of acetylsalicylic acid as part of dual antiplatelet therapy following percutaneous coronary intervention?

KEY FINDINGS

A limited quantity of evidence was identified on aspirin doses as part of dual antiplatelet therapy however one large, well-conducted randomized controlled trial included in this report directly addressed this research question. This international trial reported no differences in the outcomes of cardiovascular death, myocardial infarction, stroke, stent thrombosis, or major bleeding outcomes between high-dose (300 – 325 mg per day) and low-dose (75 – 100 mg per day) aspirin in dual antiplatelet therapy regimens with clopidogrel. During the three-month follow-up, evidence of a statistically significant increase in recurrent ischemia was reported for patients receiving the low aspirin dose as part of the dual antiplatelet therapy regimens. A retrospective observational study also did not observe statistically significant differences for dual antiplatelet therapy patients in cardiovascular death, myocardial infarction, stroke or major bleeding outcomes between high-dose (325 mg per day) and low-dose (81 mg per day) aspirin. Both studies observed a significant increase in minor bleeding outcomes for patients in this population receiving the high-dose aspirin regimens following percutaneous coronary intervention management. A third study, with important methodological limitations, was consistent with the large randomized controlled trial and did not observe a statistically significant difference in the occurrence of stent thrombosis between patients receiving a moderate/high-dose (162 – 325 mg per day) or a low-dose (81 mg per day) aspirin as part of a dual antiplatelet therapy regimen. The evidence presented in this report was therefore consistent in that low-dose aspirin as part of dual antiplatelet therapy did not increase incidence of cardiovascular death, myocardial infarction, stroke, or stent thrombosis however higher-dose aspirin increased the frequency of bleeding complications without any clear benefit.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, Medline via OVID, EMBASE via OVID, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. The search was also limited to English language documents published between Jan 1, 2010 and Nov 23, 2016.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Adults requiring antiplatelet therapy following percutaneous coronary intervention with stenting
Intervention	P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor) in combination with acetylsalicylic acid (ASA)
Comparator	Different doses of ASA as part of combination treatment with P2Y12 inhibitors High: (≥ 300 mg daily) Moderate (>100 to < 300 mg) Low (≤ 100 mg)
Outcomes	Stent thrombosis, urgent target vessel revascularization, major adverse cardiovascular and cerebrovascular events (MACCEs, including myocardial infarction, stroke, and death), bleeding (major or minor), cardiovascular death, total mortality
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010.

Critical Appraisal of Individual Studies

Randomized controlled trials (RCTs) and non-randomized studies (NRSs) were critically appraised using the Downs and Black checklist.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 730 citations were identified in the literature search. Following screening of titles and abstracts, 713 citations were excluded and 17 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 19 publications were excluded for various reasons, while three publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

A tabulated summary of study characteristics is provided in Appendix 2.

Study Design

One study published in 2010 met the inclusion criteria and was a two by two factorial RCT that resulted in four treatment groups that were followed for 30 days.[3]

Two additional studies met the inclusion criteria that were NRSs. The most recent, published in 2015, was a post-hoc analysis of a prospective observational study. Patients in this study were prescribed different doses of aspirin as part of DAPT at the discretion of the attending physician. Follow-up in this NRS was six months.[7] Lotfi et al., published in 2011, followed a cohort of DAPT patients on low-dose aspirin and then compared this group to data on high-dose aspirin DAPT patients from a previously published cohort of patients. While the follow-up for this observational study is not well defined this study has outcome data on at least some patients over one year.[8]

Country of Origin

The RCT included in this report took place in 597 centres located in 39 countries,[3] while both non-randomized studies took place in the US.[7,8]

Patient Population

Patients in the RCT were patients presenting with symptoms compatible with ACS (with or without ST-segment elevation). Electrocardiogram evidence of ischemia or raised troponin I or troponin T biomarkers were additional inclusion criteria. Importantly, the additional inclusion requirement was a coronary angiographic assessment with a plan to perform PCI no later than 72 hour following randomization. An assessment of the original 25,086 randomized patients was also published,[9] however 31% of these patients did not end up undergoing PCI for a variety of reasons. Of the patients that did not undergo PCI, 45.0% had no clinically significant coronary artery disease, 23.8% underwent coronary-artery bypass grafting, and 31.2% were not candidates for any type of revascularization. The RCT identified for this report was an analysis of 17,263 patients that did undergo PCI, 95% of whom received a stent.[3] The exclusion criteria for this RCT was active or increased risk of bleeding.[3]

The patients in the NRSs identified in this report also underwent PCI.[7,8] Xian et al. (2015) examined 10,213 patients from the TRANSLATE-ACS study who were MI patients managed with PCI. Death in hospital, discharged without ASA prescribed, missing ASA dose information, no stent implantation, incomplete follow-up, and an ASA dose other than 81 or 325 mg per day were the criteria used to exclude patients from this study.[7] The patient population from the 2011 NRS consisted of 5,187 consecutive patients who received at least one stent implantation during the study period. This case series data was then compared to data from a published network meta-analysis of 12,973 patients that took part in 24 different RCTs designed to compare different stents.[8]

Interventions and Comparators

The identified RCT compared two doses of clopidogrel and two doses of ASA creating four patient treatment groups. The distribution of random patient allocation was designed to be equivalent between these groups. Baseline characteristics and patient numbers remained well matched for randomized patients that underwent PCI. Two patient groups received a clopidogrel dose of a day one loading dose of 600 mg, followed by 150 mg per day from day two to day seven, followed by 75 mg per day from day eight to day 30. The other two treatment groups were assigned to receive a day one loading dose of 300 mg clopidogrel, followed by 75 mg per day from days two to 30. All four treatment groups received an ASA loading dose of at least 300 mg followed by 300 – 325 mg per day for two groups and 75 – 100 mg per day for the other two groups until day 30.[3]

Xian et al. followed patients on post-discharge DAPT with either 325 mg ASA or 81 mg ASA daily. All patients were also prescribed an undefined dose of clopidogrel, prasugrel, or ticagrelor as part of DAPT therapy. Statistically significant differences were observed between low and high-dose ASA patient groups and the adenosine diphosphate (ADP) receptor inhibitor received as part of DAPT.[7] The other NRS examined one cohort of patients that received a loading dose of clopidogrel of 300 or 600 mg followed by 75 mg daily as part of DAPT. This group received a loading dose of 324 mg ASA followed by 81 mg daily. The cohort to which this group was compared was less well documented with no reported data on clopidogrel dose or ASA loading dose. This cohort received 162 – 325 mg per day of ASA as part of DAPT.[8]

Outcomes

The primary outcome in the RCT was a composite of cardiovascular death, MI, or stroke that occurred between randomization and day 30. The secondary outcomes of this study were the primary outcome as individual components; that is cardiovascular death, MI, or stroke. Additional secondary outcomes were, the primary outcome plus patients with recurrent ischemia, and definite (i.e., angiographically confirmed) stent thrombosis. The primary safety outcome was major bleeding, which was defined as severe bleeding and other major bleeding. Severe bleeding was defined as fatal, leading to a drop in hemoglobin of ≥ 5 g/dL, significant hypotension requiring inotropes or surgery, symptomatic intracranial hemorrhage, or requiring ≥ 4 units of red blood cells or whole blood equivalents. Other major bleeding was defined as significantly disabling, intraocular bleeding, or requiring 2 or 3 units of red blood cells or whole blood equivalents. Minor bleeding was defined as any other bleeding requiring modification of the drug regimen.[3]

Xian et al. reported the composite of death, MI, stroke, or unplanned revascularization (major adverse cardiac event, MACE) from discharge to six months. This study also reported bleeding events as defined by the Bleeding Academic Research Consortium (BARC) from discharge to six months. Any BARC bleeding, minor BARC bleeding (types 1 or 2 bleeding that did not require hospitalization), and any other BARC bleeding that required hospitalization were analyzed as outcomes. BARC bleeding classifications were defined by Xian et al as: type 0, no bleeding; type 1, bleeding requiring no intervention; type 2, overt actionable bleeding; type 3, clinical, laboratory and imaging evidence of bleeding requiring specific interventions; type 4, coronary artery bypass graft-related bleeding; type 5, fatal bleeding.[7]

Lotfi et al. reported the incidence of defined stent thrombosis (DST) as defined by the Academic Research Consortium (ARC) classification. DST was angiographically or pathologically confirmed occlusive or nonocclusive thrombus that originated in the stent or in the segment 5mm proximal or distal to the stent. DST also required one of the following: acute onset of ischemic symptoms; new ischemic electrocardiogram changes; or typical rise and fall of cardiac markers. This outcome data was available on the comparative cohort as the cohort data was from RCTs comparing different stents.[8]

Summary of Critical Appraisal

A tabulated summary of the critical appraisal is provided in Appendix 3.

The RCT was a large study with sufficient enrollment as determined a priori however the power calculation was done for the originally intended patient population. Despite the 31% of patients excluded in the analysis for not undergoing PCI as intended, the study had greater than 90%

power to detect an 18.2% relative reduction in primary event rate, assuming a primary outcome event rate of 4.5% in the standard treatment group. A flowchart of patient recruitment and follow-up for this study was included, in addition to tabulated patient characteristics. A statistical analysis of patient characteristics between groups was not provided. While outcome assessments for the trial were blinded, and clopidogrel dose was double-blinded, ASA dose was open-label. Sufficient methodological details were reported for allocation concealment, randomization, statistical methods, patient eligibility, the role of blinded investigators, interventions, and outcomes. A discussion on study limitations was also provided. A conflict of interest (COI) statement reported pharmaceutical industry funding. The findings of this study are limited by a follow-up of 30 days.

The NRSs are both inherently limited by their retrospective observational design. Xian et al.[7] included tabulated patient characteristics however the baseline characteristics had statistically significant differences including between-group differences in the ADP inhibitor used as part of DAPT. A clear definition of patient eligibility, the intervention, outcomes, and statistical methods was provided. While the authors report an intent-to-treat (ITT) analysis, insufficient details on how missing data or protocol deviations were handled. A COI statement reported industry funding for the study. The authors of this study used statistical adjustment to account for potential confounders, however the patients were allocated to treatment group based upon the discretion of the physician.[7] Lotfi et al.[8] was limited by the study design where the comparator cohort data was published as part of a separate meta-analysis. Limited patient characteristics and intervention details on this comparator group were provided. There was also a lack of information on the follow-up of patients, and an insufficiently defined patient eligibility. While the outcome of stent thrombosis in this study was well defined, this was the only reported outcome. No information on bleeding or any other adverse event data was provided. A comprehensive discussion on these limitations was provided by the authors.[8]

Summary of Findings

What is the comparative clinical benefit and harm of different doses of acetylsalicylic acid as part of dual antiplatelet therapy following percutaneous coronary intervention?

A tabulated summary of findings is provided in Appendix 4.

The RCT, Mehta et al. (2010),[3] found no statistically significant differences between a high-dose (300 – 325 mg) or a low-dose (75 – 100 mg) ASA as part of DAPT following PCI in the primary outcome of cardiovascular death, MI, or stroke, or secondary outcomes including major bleeding, severe bleeding, total mortality, MI, CV death, stent thrombosis, or stroke. The authors did not comment on the clinical importance of the statistically significant findings of greater recurrent ischaemia in the low-dose ASA group (0.4 vs 0.2%) and greater minor bleeding in the high-dose ASA group (5.0 vs 4.3%). The authors interpret their findings as suggestive of no benefit or harm of high-dose ASA as part of DAPT. High-dose ASA patients allocated to high-dose clopidogrel experienced a primary outcome rate of 3.5% while high-dose ASA patients allocated to standard dose clopidogrel experienced a primary outcome rate of 4.8% in 30 days. The authors recommended a conservative interpretation of the clinical significance of this significant statistical interaction ($P = 0.026$) between clopidogrel and ASA dose comparisons. A similar statistically significant difference was not observed between low-dose ASA patient groups.[3]

The NRS data from Xian et al.[7] did not observe a statistically significant difference in MACE outcomes between 325 mg ASA per day and 81 mg ASA per day. This study did however find evidence suggestive of increased minor BARC bleeding (types 1 and 2) for discharged PCI patients managed with high-dose ASA as part of DAPT. This finding remained statistically significant for observations of overall BARC bleeding when the hazard ratio (HR) was adjusted using weighted known covariates.[7] The reported rates of minor BARC bleeding, of 20.7% overall, were notably greater in Xian et al., than the minor bleeding rates of 4.7% overall reported in Mehta et al. which may have reflected different bleeding outcome definitions and different follow-up times.[3,7] A subpopulation analysis of any BARC bleeding and minor BARC bleeding in Xian et al. found statistically significantly less bleeding for low-dose ASA patients taking prasugrel or ticagrelor DAPT as compared to these drugs taken with high-dose ASA. This difference in bleeding outcomes between ASA doses was not statistically significant for patients taking clopidogrel and ASA DAPT. No statistically significant differences in MACE outcomes between low-dose and high-dose ASA with any DAPT regimen were observed.

There was no evidence of a statistically significant difference between stent recipients taking a moderate/high-dose (162 – 325 mg) and a low-dose (81 mg) of ASA in outcomes of DST as reported by Lotfi et al. (2011).[8] While there was significantly less DST at 30 days for drug-eluting stent (DES) recipients on low-dose ASA this difference was not statistically significant beyond 30 days. No bleeding related outcomes were reported in this study.[8]

Limitations

A single well designed, sufficiently powered RCT was identified that directly addressed the research question. This RCT was limited by a follow-up of 30 days. While outcome assessments of this RCT were blinded, ASA doses were open-label. The other evidence identified here from two studies is limited by observational design.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One high-quality, sufficiently powered RCT demonstrated no statistically significant differences in cardiovascular death, MI, stroke or major bleeding complications between high-dose and low-dose ASA as part of DAPT.[3] Mehta et al.[9] also demonstrated in a separate analysis of the same RCT data that these aspirin doses were not observed to be statistically significantly different in a population that was planned for PCI, but did not necessarily undergo PCI within 72 hours after randomization. The authors of these analyses acknowledge that it can not be determined at presentation whether a patient will receive PCI, however in the case of ASA dose as part of DAPT no statistically significant differences were found whether patients underwent PCI or not.[3,9] Both analyses found a statistically significant increase in recurrent ischemia for the low-dose ASA groups, offset by a statistically significant increase in minor bleeding for the high-dose ASA groups.[3,9] Some expert interpretations reported that these findings support the use of low-dose aspirin as part of DAPT,[10,11] except perhaps in cases where there is concern for recurrent ischemia.[1] The findings of two NRSs included in this report are consistent with the conclusions of this RCT.[7,8] One NRS found no evidence for statistically significant differences in MACE or major bleeding outcomes but also observed evidence of increased minor bleeding for patients using a high-dose ASA DAPT regimen.[7] Another retrospective observational study with some important methodological limitations was identified and, similar to the identified RCT, did not find evidence of increased stent thrombosis in patients receiving a low-dose ASA DAPT regimen.[8] The evidence presented here is consistent with evidence from two post hoc trial data analyses identified in a previous CADTH technology report from 2010.[5] These analyses examined data from different trials and were assessed as being of fair quality. The analyses did not identify statistically significant differences in ASA doses as part of DAPT with regards to a composite outcome of cardiovascular death, MI, or stroke. One analyses found a statistically significant increase in major bleeding complications and life-threatening bleeding complications in patients receiving ≥ 200 mg per day ASA with clopidogrel as compared to patients receiving 101 to 199 mg per day ASA and patients receiving ≤ 100 mg per day ASA.[5] The limited evidence identified in this report therefore also supports low-dose aspirin (< 100 mg per day) as part of dual antiplatelet therapy as it did not increase incidence of cardiovascular death, myocardial infarction, stroke, or stent thrombosis. Higher-dose aspirin (> 300 mg per day) increased the frequency of adverse bleeding outcomes without any clear benefit.

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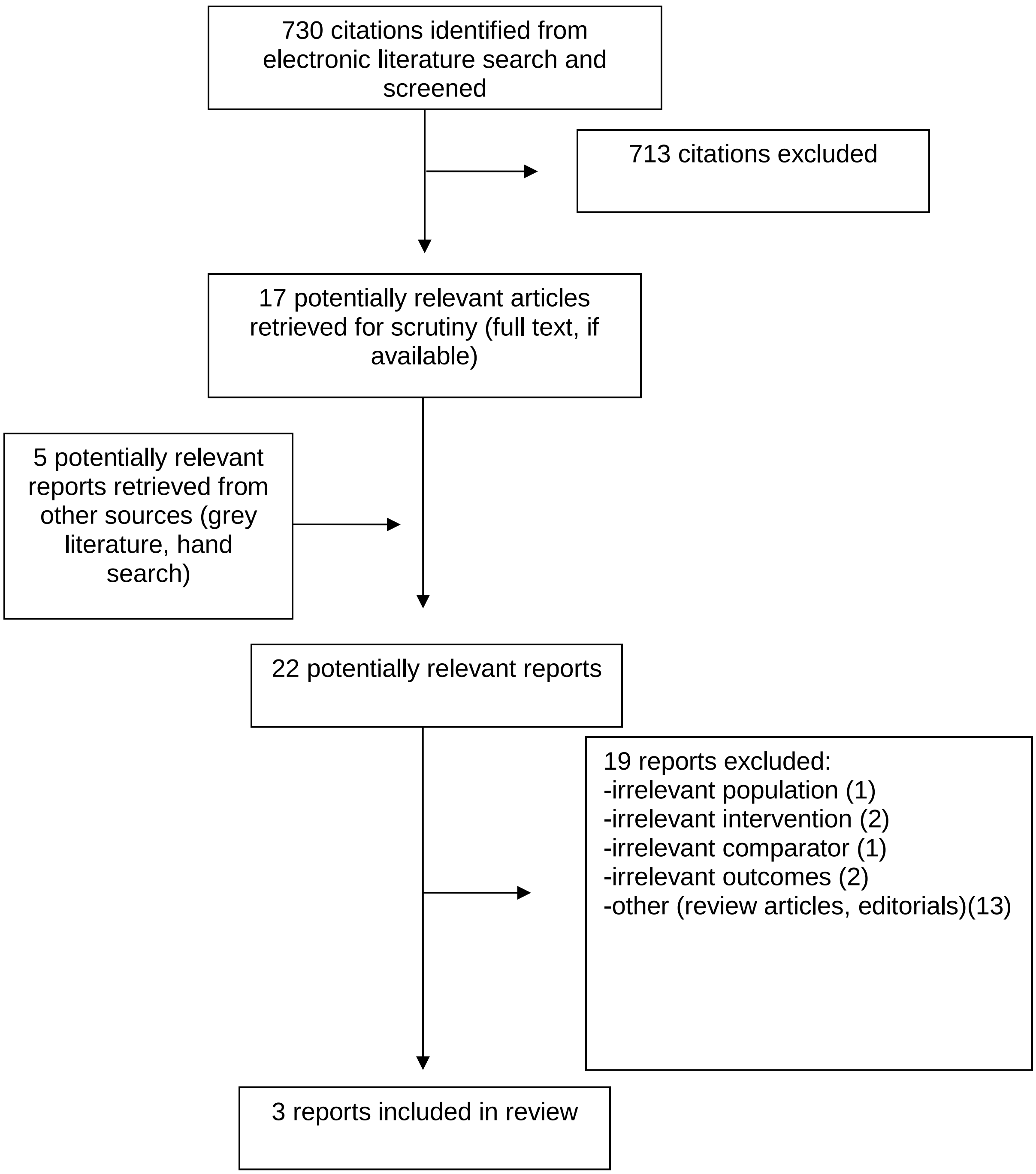
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A2.1: Characteristics of Included RCT

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Mehta, 2010,[3] in 39 countries. CURRENT-OASIS 7 trial (NCT00335452)	2x2 factorial RCT (all four dose combinations were equally randomized) FU = 30days	ACS patients with ECG evidence of ischemia or raised biomarkers (troponin I or T) that underwent PCI (n = 25086) Exclusions: active or increased risk of bleeding	**1. Double-dose Clopidogrel** -Day 1 – 600mg loading dose -Day 2 to 7 – 150mg q.d. - Day 8 to 30 – 75mg q.d. **2. High-dose ASA** - Day 1 – ≥ 300mg loading dose - Day 2 to 30 – 300-325mg q.d.	**1. Standard-dose Clopidogrel** - Day 1 – 300mg loading dose - Day 2 to 7 – 75mg q.d. - Day 8 to 30 – 75mg q.d. **2. Low-dose ASA** - Day 1 – ≥ 300mg loading dose -Day 2 to 30 – 75-100mg q.d.	**Primary Outcome** • Composite of cardiovascular death, MI, or stroke **Secondary Outcomes** • Primary outcome components • Primary outcome plus recurrent ischemia • Definite stent thrombosis

ACS = acute coronary syndrome; ASA = acetylsalicylic acid; ECG = electrocardiogram; FU = follow-up; MI = myocardial infarction; PCI = percutaneous coronary interventions; q.d. = once per day; RCT = randomized controlled trial.

Table A2.2: Characteristics of Included NRSs

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Xian, 2015,[7] US, Data from TRANSLATE-ACS (NCT01088503)	Post-hoc analysis of a prospective observational study FU = 6months	MI patients managed with PCI (n = 10213) Exclusions: Died in hospital, not discharged on aspirin, missing aspirin information, no stent implantation, incomplete follow-up, aspirin dose other than 81 or 325mg q.d.	Postdischarge DAPT: 325mg ASA q.d. (n = 6387) w/ one of clopidogrel, prasugrel, or ticagrelor	Postdischarge DAPT: 81mg ASA q.d (n = 3826) w/ one of clopidogrel, prasugrel, or ticagrelor	• MACE from discharge to six months • BARC from discharge to six months
Lotfi, 2011,[8] US	Case-control study. Observational	Patients who received at least one stent	**Clopidogrel** - loading dose 300 or 600mg	**Clopidogrel** NR	• Definite stent thrombosis categorized as

Table A2.2: Characteristics of Included NRSs					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
	cohort compared to data for high-dose aspririn controls taken from a previously published collaborative network MA FU = undefined but has data on patients over 1year	implantation.	- DAPT 75mg q.d. **ASA** - loading dose 324mg - DAPT 81mg q.d. (n = 5187)	**ASA** - loading dose NR - DAPT 162 - 325mg q.d. (n = 12 973)	acute (0 – 24 hours), subacute (24 – 30 days), late (30 days – 1 year), and very late (> 1 year)

ASA = acetylsalicylic acid; BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; FU = follow-up; MA = meta-analysis; MACE = composite outcome of death, MI, stroke, and unplanned revascularization; NR = not reported; MI = myocardial infarction; PCI = percutaneous coronary intervention; q.d. = once per day.

APPENDIX 3: Critical Appraisal of Included Publications

Table A3.1: Strengths and Limitations of Randomized Controlled Trials and Non-randomized studies using Downs and Black Checklist[6]

Strengths	Limitations
RCT	
Mehta et al., 2010[3]	
• Large international study • CONSORT diagram for patient recruitment/enrollment • Patient characteristics tabulated • Outcome assessment masked to aspirin dose • Allocation concealment methodology described • Statistical methods described • Randomization methodology described • Role of blinded investigators outlined • Clearly defined patient eligibility • Clearly defined intervention • Clearly defined outcomes • Statistical power determined a priori, based on whole population but subpopulation was sufficiently large • ITT analysis -did not explain how missing or protocol deviation data was handled, however very few lost to follow-up (3 patients) • Discussion on study limitations • Adverse events discussed and quantified • COI statement	• Patient characteristics not evaluated for significant differences • Clopidogrel dose double-blind but ASA dose was open-label • Subpopulation study (patients who underwent PCI) of an RCT population with intent to undergo PCI • Limited to 30 day follow-up • Industry funded study
NRS	
Xian et al., 2015[7]	
• Large multicenter study • Patient characteristics tabulated • Statistical methods described • Clearly defined patient eligibility • Clearly defined intervention • Clearly defined outcomes • ITT analysis -did not explain how missing or protocol deviation data was handled • Statistical power calculation presented • Adverse events discussed and quantified • COI statement • Comprehensive discussion on study limitations	• Baseline patient characteristics contained statistically significant differences between groups (including in ADP receptor inhibitor used) • Retrospective observational study • Industry funded study • Allocation based upon physician discretion
Lotfi et al., 2011[8]	
• Patient characteristics tabulated • Clearly defined outcomes • Comprehensive discussion on study limitations	• Single center study • Indirect group comparison • Limited control population information reported

Table A3.1: Strengths and Limitations of Randomized Controlled Trials and Non-randomized studies using Downs and Black Checklist[6]	
Strengths	**Limitations**
	• Retrospective observational study • Patient eligibility not specified • Intervention for comparator group not well described • Unknown loss to follow-up – no mention of ITT analysis • No adverse event outcomes

ADP = adenosine diphosphate; ASA = acetylsalicylic acid; ITT = intent-to-treat.

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A4.1: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
RCT	
Mehta et al., 2010[3]	
Cardiovascular death, MI, or stroke n/N (%) (*p* = 0.76) ASA (300 – 325 mg q.d.): 356/8624 (4.2%) ASA (75 – 100 mg q.d.): 366/8639 (4.1%) Cardiovascular death, MI, or stroke or recurrent ischemia n/N (%) (*p* = 0.24) ASA (300 – 325 mg q.d.): 342/8624 (4.0%) ASA (75 – 100 mg q.d.): 374/8639 (4.3%) CV death n/N (%) (*p* = 0.38) ASA (300 – 325 mg q.d.): 156/8624 (1.8%) ASA (75 – 100 mg q.d.): 173/8639 (2.0%) MI n/N (%) (*p* = 0.75) ASA (300 – 325 mg q.d.): 175/8624 (2.0%) ASA (75 – 100 mg q.d.): 181/8639 (2.1%) Stroke n/N (%) (*p* = 0.45) ASA (300 – 325 mg q.d.): 35/8624 (0.4%) ASA (75 – 100 mg q.d.): 29/8639 (0.3%) Major bleeding (TIMI) n/N (%) (*p* = 0.20) ASA (300 – 325 mg q.d.): 128/8624 (1.5%) ASA (75 – 100 mg q.d.): 110/8639 (1.3%) Major bleeding (CURRENT) n/N (%) (*p* = 0.32) ASA (300 – 325 mg q.d.): 120/8624 (1.4%) ASA (75 – 100 mg q.d.): 105/8639 (1.2%) Total mortality n/N (%) (*p* = 0.20) ASA (300 – 325 mg q.d.): 160/8624 (1.9%) ASA (75 – 100 mg q.d.): 185/8639 (2.1%) Recurrent ischemia n/N (%) (*p* = 0.0083) ASA (300 – 325 mg q.d.): 15/8624 (0.2%) ASA (75 – 100 mg q.d.): 34/8639 (0.4%) Minor bleeding - (pre and post PCI) n/N (%) (*p* = 0.019) ASA (300 – 325 mg q.d.): 433/8624 (5.0%) ASA (75 – 100 mg q.d.): 370/8639 (4.3%)	"In our study of more than 17 000 patients undergoing PCI in which aspirin dose was randomised, we recorded no difference between high-dose and low-dose aspirin for major bleeding, stent thrombosis, or major cardiovascular events. Although we detected a nominally significant statistical interaction between clopidogrel and aspirin dose comparisons, such an observation was unexpected and does not have a known biological mechanism. Therefore, we recommend a conservative interpretation of its clinical significance. If clinicians choose to use high-dose aspirin, our results suggest no harm (nor benefit) compared with low-dose aspirin, which implies that either dose is a reasonable option after PCI." (pp. 1239) "There was no difference between the aspirin dose groups in the secondary composite outcome of cardiovascular death, myocardial infarction, stroke, or refractory ischaemia, with consistency in the results for the individual components of the primary outcome" (pp. 1237) The authors do not comment on the statistically significant difference in recurrent ischaemia or minor bleeding between ASA dose groups

Table A4.1: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
NRS	
Xian et al., 2015[7]	
MACE n/N (%) ASA (325 mg q.d.): 522/6387 (8.2%) ASA (81 mg q.d.): 352/3826 (9.2%) HR (95% CI): 0.89 (0.77, 1.02)* Adjusted HR (95% CI): 0.99 (0.85, 1.17)** Any BARC bleeding n/N (%) ASA (325 mg q.d.): 1547/6387 (24.2%) ASA (81 mg q.d.): 870/3826 (22.7%) HR (95% CI): 1.09 (0.98, 1.20)* Adjusted HR (95% CI): 1.19 (1.06, 1.33)** Higher BARC bleeding n/N (%) ASA (325 mg q.d.): 178/6387 (2.8%) ASA (81 mg q.d.): 124/3826 (3.2%) OR (95% CI): 0.88 (0.70, 1.10)* Adjusted OR (95% CI): 1.22 (0.87, 1.70)** Lower BARC bleeding n/N (%) ASA (325 mg q.d.): 1369/6387 (21.4%) ASA (81 mg q.d.): 746/3826 (19.5%) OR (95% CI): 1.12 (1.01, 1.25)* Adjusted OR (95% CI): 1.19 (1.05, 1.34)** Any BARC bleeding subpopulation analyses*** Clopidogrel OR (95% CI): 1.10 (0.95, 1.27) Prasugrel or Ticagrelor OR (95% CI): 1.39 (1.15, 1.67) Age < 65years OR (95% CI): 1.21 (1.07, 1.38) Age ≥ 65 years OR (95% CI): 1.14 (0.94, 1.39) Male OR (95% CI): 1.20 (1.05, 1.38) Female OR (95% CI): 1.19 (0.97, 1.47) Home aspirin use OR (95% CI): 1.28 (1.06, 1.55) No home aspirin use OR (95% CI): 1.13 (0.98, 1.30) Minor BARC bleeding subpopulation analyses*** Clopidogrel OR (95% CI): 1.10 (0.94, 1.29) Prasugrel or Ticagrelor OR (95% CI): 1.38 (1.15, 1.66) Age < 65years	"… our data suggest no added benefit and potential harm of bleeding events associated with high-dose aspirin, regardless of whether clopidogrel or a more potent ADP receptor inhibitor was used. In light of these results, low-dose aspirin appears to be a reasonable option for long-term maintenance therapy following PCI for all patients treated with clopidogrel, prasugrel, or ticagrelor." (pp. 179) "Importantly, aspirin doses were not randomly assigned. We were unable to determine the rationale for drug choice or treatment dosing. We included in the propensity model a comprehensive list of covariates, including baseline patient and clinical risk factors, bleeding history, and home medication use to minimize the impact of potential treatment selection on longitudinal clinical outcomes; nevertheless, treatment selection and unmeasured confounding may bias outcome comparisons." (pp. 179)

Table A4.1: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
OR (95% CI): 1.22 (1.07, 1.40) Age ≥ 65 years OR (95% CI): 1.15 (0.93, 1.42) Male OR (95% CI): 1.23 (1.07, 1.41) Female OR (95% CI): 1.15 (0.93, 1.41) Home aspirin use OR (95% CI): 1.26 (1.03, 1.54) No home aspirin use OR (95% CI): 1.16 (1.00, 1.35) No additional subpopulation outcome differences were statistically significant including all subpopulations in outcomes of higher BARC bleeding * (High-dose vs Low-dose) ** Adjusted ratio (High-dose vs Low-dose) adjusted for potential confounding with weighted covariates *** Adjusted OR > 1 favours low-dose ASA	
Lotfi et al., 2011[8]	
Overall DST (p = 0.39) ASA (162 – 325 mg q.d.): 0.72% ASA (81 mg q.d.): 0.60% DST at one year (p = 0.07) ASA (162 – 325 mg q.d.): 1.08% ASA (81 mg q.d.): 0.76% DST at 30 days for DES (p = 0.01) ASA (162 – 325 mg q.d.): 0.74% ASA (81 mg q.d.): 0.34% DST beyond 30 days for DES (p = 0.89) ASA (162 – 325 mg q.d.): 0.36% ASA (81 mg q.d.): 0.38% Homogeneity test for effect modification demonstrated no statistically significant effect on DST from aspirin type on: Stent type (DES or BMS): (p = 0.42) Time to event: (p = 0.09)	"Low-dose aspirin therapy in combination with clopidogrel following implantation of either BMS or DES in our cohort does not appear to increase the risk of DST compared to a higher-dose aspirin regimen." (pp. 567)

ASA = acetylsalicylic acid; BARC = Bleeding Academic Research Consortium; BMS = bare metal stent; CI = confidence interval; DES = drug-eluting stent; DST = definite stent thrombosis; MACE = composite outcome of death, MI, stroke, and unplanned revascularization; q.d. = once per day.